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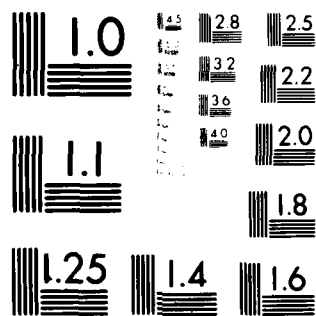
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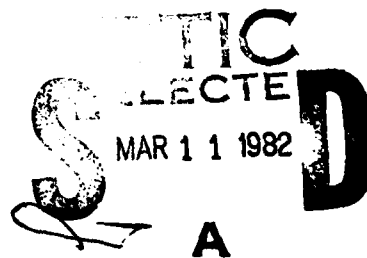
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THE BIOLOGICAL EFFECTS OF NONIONIZING RADIATION

J.B. BATEMAN*

29 December 1981

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)
This is a critical report on the L.H. Gray Memorial Conference held in Oxford, 13-16 July 1981. The Conference was entitled "Biological Action of Radiofrequency, Microwave and Ultrasonic Radiations." The report provides a background identifying the field of interest in broader terms, intended for the general reader. It is then pointed out that the conference was mainly directed toward research and practice related to the possible value of nonionizing radiations in cancer therapy. There were, however, tutorial lectures of a fairly general character and some discussion of biological effects not necessarily arising from production of heat in irradiated tissues.

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THE BIOLOGICAL EFFECTS OF NONIONIZING RADIATION

The Tenth L.H. Grey Memorial Conference, on the biological effects of nonionizing radiation, was held in Oxford, England, from 13 to 16 July 1981. It was sponsored by the L.H. Grey Memorial Trust, founded in 1967 by the British Institute of Radiology, the Association for Radiation Research, and the Hospital Physicists' Association in honor of the late H.L. Grey, who is known for his work on the biological effects of ionizing radiation and the problem of neutron dosimetry. The conference was well organized and well attended. Among the participants was A.P. Sarvazyan of the USSR Academy of Sciences.

The substance of the conference was somewhat narrower than the title would suggest. In the author's opinion, it might more accurately have been subtitled: "Principles and Practice of Selective Heating in the Treatment of Cancer." This report deals, first, with selected conference proceedings related directly to matters implied by this more explicit title; second, with the vexed question of "prethermal" effects. In the author's opinion this controversial second topic, though represented in several contributions, received far less than its due of knowledgeable discussion. In the course of the report the author has occasionally tried to place the proceedings in perspective by providing some background comment and a few key references. The affiliations of the participants mentioned in the report are listed in the Appendix.

Nomenclature and Abbreviations

In this report, some unconventional terminology is employed in order to clarify the ideas being presented. The words "phantom" and "model" for example, sometimes seemed to be used interchangeably during the conference. Here, "phantom" will mean an imaginary model used for theory, "model" will be an actual physical assembly having certain points of resemblance to the system it is supposed to mimic, "computer model" is retained although it really means computer phantom. The following nonstandard abbreviations are used: microwave = m-wave; radiowave = r-wave; radio and microwaves = rm-waves; radiofrequency = rf; ultrasonic radiation = u-sound; ultrasonic = u-soni . In addition, the phrase "deposition of heat" is avoided in "energy conversion" to mean conversion of radiant energy to heat.

I. HOW TO INVESTIGATE THE THERAPEUTIC USES OF HEAT, ESPECIALLY IN CANCER

All living cells can be destroyed by heat. Can heat be supplied selectively to destroy unwanted organs or tissues while preserving others from injury? There are two possibilities. First, if one tissue—a tumor, say—happens to be more sensitive to heat than the healthy parts of the body, and by a sufficient margin, it might be disposed of simply by inducing fever. A hot water bath, a hot room, or a chemical or biological pyrogen might suffice. Second, whether or not the tumor is differentially sensitive, it might be destroyed if means could be found to heat it to a lethal temperature without injuring the surrounding

normal tissues. According to N.W. Bleehan, this was the method used
by Hippocrates, with the aid of a hot iron. Hippocrates, by the way,
is by no means out of date. A Mayo Clinic surgeon recalls that the
late Virgil Counsellor, for whom he worked during his early days at
the clinic, "used cautery freely in destruction of tumors, especially
in the bladder. When doing so, if the smoke got in his way, he would
take his mask down, blow it (sic) away and continue burning. The patient
always did well." (Beahrs 1981). This was selective heating par excel-
lence. More recently, ultrasound and nonionizing electromagnetic ra-
diations have entered the picture because of their ability to penetrate
biological structures, where their energy is converted into heat by
a process dubbed "deposition."

Enough theoretical and experimental information exists to justify
the conclusion that the fraction of incident energy converted into heat
by these radiations in any part of the body depends not only on the
physical characteristics of the generator and its mode of linkage to
the body, but also on the shape of the body and the spatial arrangement
of organs, tissues, and cells within it. To illustrate this crudely,
the depth of penetration at which the incident intensity is reduced
e-fold decreases with increasing radio or microwave frequency. For in-
stance, it might be about 13 cm for muscle and 130 cm for fat at 30 MHz
decreasing to 0.1 cm and 0.4 cm respectively at 10 GHz (Martin 174,
1974, 1975). The actual spatio-temporal pattern of thermal conversion,
however, is much more complicated in the highly heterogeneous animal
body. Heating will be notably nonuniform, even to the point at which
there may be focal accumulations of heat or "hot spots" under some con-
ditions (Kritikos and Schwan 1975, 1976). It has occurred to many people
that this nonuniformity might be manipulated to the benefit of the cancer
patient, with or without the aid of ionizing radiation or drugs. A
large part of the conference was devoted to progress reports of work
related in some way to this end.

Excluding empirical attempts that would have little chance of success
in such a highly convoluted field, there are two major requirements
for proper testing of the idea just broached: (1) the problem must
be solved of specifying, and putting into operation, the means of pro-
ducing a defined spatio-temporal pattern of desired increases of tempera-
ture in the body; (2) the biological consequences of doing this must
be established and evaluated within the framework of their contribution
to the desired clinical outcome, either applied separately or as an
adjunct to favorable responses produced by other means.

There are, of course, any number of problem subsets with a lot of
feedback. If a systematic program were feasible—and there are no signs
of such a program on the horizon—it might take the form indicated in
(1) and (2) below for radio and microwaves. It would be similar for
ultrasound.

(1) Physical Control

(a) Dielectric properties of biological systems and their constitu-
ents: as a function of frequency and temperature and as a function

of degree and scale of organization—e.g., from molecules to animals on a physical scale, and from "bits of meat" to physiologically normal entities on a biological scale.

(b) Thermal properties of biological systems and thermal transport mechanisms.

(c) Theory of thermal conversion in dielectrics composed of structures and substructures of known dielectric properties assembled in specified spatial arrangements, as a function of the physical parameters of the monochromatic or polychromatic incident radiation: frequency, modulation, field properties at the position of the target, distortions of field produced by the presence of the target, etc.

(d) Theory of spatio-temporal temperature patterns resulting from thermal conversion, as a function of the various modes of heat transport and their spatio-temporal variation: radiation, conduction, thermal diffusion (Soret effect), convection, fluid flow, scaling—extrapolation from mouse to man.

(e) Experimental study of temperature distribution in models (called "phantoms" by some investigators) with attempts to check the theory and to simulate the conditions obtaining in the live animal.

(f) Measurements of temperature distribution in small animals subjected to hyperthermia generated in different ways: methods of measuring temperature without field distortion; whole-body versus local hyperthemia; comparison of different physical heat sources; normal versus pathological states; conditions for selective heating of tumors; degree of spatial resolution attainable.

(g) Temperature distribution in man when heated in different ways: direct measurements to confront predictions derived from theory, models, and smaller animals.

(2) Biological Control

(a) Thermal sensitivities of normal and abnormal tissues: optimum temperature differences for optimum injury to tumor and acceptable level of damage to normal tissues; dependence of thermal sensitivity on local conditions such as partial pressure of oxygen, pH, metabolite accumulation, etc.

(b) Physiological responses to general or local hyperthermia in man: circulatory changes locally or centrally mediated. Changes in endocrine balance brought about by central nervous system responses and their sequelae, such as undesired disturbances of thermostasis or enhanced corticosteroid activity. Direct thermal effects on the hypothalamus in the irradiated brain. Immunological and hematological effects.

(c) Clinical and laboratory studies of the effects of hyperthermia on tumors.

(d) Modifications by hyperthermia of the effectiveness of other therapeutic measures, principally ionizing radiation and drugs.

II. HYPERTHERMIA: PHYSICAL AND BIOLOGICAL CONTROL AND THERAPEUTICS

(1) Introduction

The conference was begun by a session entitled "History and Tutorial," in which four speakers reviewed u-sonic and rm-wave hyperthermia (H.P. Schwan), rm-wave interactions with tissues (E.H. Grant, conference co-organizer), u-sound biophysics (C.R. Hill) and treatment of cancer by rm-wave hyperthermia (N.M. Bleehan). Schwan's wide-ranging remarks, with his references to pioneering work too often forgotten or ignored nowadays (Esau, Schliephake, Paetzold, Rashewsky), were especially welcome. As an introduction for delegates from diverse disciplines, however, the papers would have been more valuable if there had been evidence of tighter prior collaboration in comparing and coordinating knowledge of the respective fields.

(2) Mechanisms of Energy Conversion

Except for the introductory sessions, the conference devoted little time to the identification of basic mechanisms of energy conversion at the molecular level. At the level of cellular assemblages, A.P. Sarvazyan summarized the contributions of different structural features to u-sonic properties. The shear modulus is extremely sensitive to cell structure while the bulk modulus is mainly of molecular origin. The bulk velocity, 1500-1700 ms^{-1}, has a very narrow range of values in normal and pathological tissues. Shear properties, such as shear viscosity, may become highly abnormal in diseases like psoriasis. The shear stresses are mainly responsible for thermal conversion in tissue; consequently there is considerable dispersion of attenuation coefficient between 2 and 20 MHz but comparatively little difference among different bulk tissues. F. Dunn pointed out that because of the nonlinearity of the equation for a u-wave propagated in a fluid, higher harmonics are generated and viscous energy dissipation is increased. In a strongly absorbing medium the amplitude approaches zero and a linear approximation can be used. Dunn applied the ratio of two coefficients in a Taylor series as a measure of nonlinearity and presented values of the ratio, B/A, for various biological media. For simple solutions the specific increment (B/A)/c, where c is concentration, has a constant low value over a wide range of solute molecular weights. Cellular structure generates high values of B/A, as illustrated by comparing red blood cells with hemoglobin solutions, or intact liver with "homogenized" liver. Evidently much structure is retained after homogenization of liver because the value of B/A was higher than that of intact red cells at the same concentration.

In the case of rm-waves at field strengths suitable for biological study and medical application, frequency is conserved, so that the frequency spectra of biological media can be characterized reliably by means of monochromatic sources. These, and the contributory mechanisms, are understood in general terms, but much detailed empirical information

on the differences between various tissues and organs is still needed.
The lability of excised tissues is a serious obstacle.

Deterioration of a tissue sample is inevitable in the time needed
for accurate dielectric measurements at several frequencies. The physical
constraints imposed also tend to preclude the possibility of maintaining
the sample in anything approaching a physiologically acceptable condition.
Consequently, it is perhaps fruitless to expect much progress in the
near future toward physiologically adequate values. A big step forward
has been made, however, with the introduction and biological application
of time domain spectroscopy. This, it is true, requires a small sample
of exactly the right dimensions to be confined in a closed measuring
cell under very "unphysiological" conditions, but a complete set of
measurements can be made in a couple of minutes. This is done by com-
paring the profile of an incident pulse with that of its own reflection
and subjecting the difference to Fourier analysis. The result is a
complete complex permittivity spectrum in the frequency domain, typically
covering the range 30 MHz to about 10 GHz. The promise of this technique
was illustrated in two papers by E.H. Grant and by R.J. Sheppard, who
found significant permittivity differences between excised tumor tissue
and the adjacent muscle, and between lens cortex and nucleus of the
normal eye. The pairs of curves diverged most clearly at the lower
frequencies, reflecting, perhaps, organizational rather than molecular
differences.

(3) Theory of Thermal Conversion in Large Anatomical Structures

There were no papers reporting important advances beyond those already
in the literature based on phantoms that simulate physical properties
and gross anatomical configurations. It may be rash to use purely theo-
retical results to predict real behavior *in vivo*. T.S. Sandhu and
H.I. Bicher pointed to the practical difficulties in establishing the
heating patterns in patients receiving rm-wave treatment. The thermal
field must be defined in a manner analogous to that of the radiation
field in terms of the width and depth of penetration at which the field
strength has been reduced to half its incident value, whereas actual
temperature measurements, being invasive, must be confined to two or
three points. The authors suggested that theoretical calculations may
have their place in a procedure that starts with actual measurements
of the energy conversion pattern in "anatomically equivalent" models.
This being established, the picture is completed theoretically by intro-
ducing the equations for heat transfer by thermal conduction and blood
flow. In the ensuing discussion, the 50% definition of the energy con-
version field was criticized as being incompatible with the complexities
of the real body. The simulation of blood vessels by plane parallel
cavities in a plane parallel model was also criticized. H.P. Schwan
thought it would be justifiable at the legally approved frequency of
2,490 MHz.

J.J. W. Lagendijk calculated the temperature profile in a large cylindrical blood vessel passing axially through a cylinder of heated tissue. The profiles presented showed a steep descent to a narrow central intravascular zone of constant temperature. The value of this rather obvious result, familiar to heat exchange engineers and physiologists, depends upon its quantitative compatibility with actual u-sonic and rm-wave heating conditions and the actual arrangement of blood vessels in tissues. The flowing blood is heated, of course. By the same token, it cools the tissue and generates temperature gradients within it. These may be undesirable if the therapeutic goal is to cause uniformly destructive heating. Dramatic regression may then be succeeded by regrowth.

The advantages of using r-waves for heating muscle to a depth of several centimeters while keeping superficial fat reasonably cool were illustrated in a theoretical study encouragingly supported by *in vivo* measurements on pigs (R.W. Hand, et al.). I missed Hand's paper and have drawn upon a published paper (Hand et al. 1980) for some details. Pancake coils carrying 27.12-MHz alternating current placed near a plane layer of skin overlying fat and muscle (the skin is neglected in the paper but mentioned in the conference abstract) would be expected to cause deep but very nonuniform heating, with sharp maxima immediately beneath each turn of the coil. Greater uniformity can be achieved by increasing the distance from coil to surface and by scanning the irradiated surface by constant motion of the coils. Blood flow in the muscle layer was included in the calculations. Hand et al. also noted that it may be advantageous to cool the skin. On the other hand, in apparent contradiction, they suggest that by combining local rf hyperthermia with a moderate systemic fever undesirable cold spots caused by blood flow might be eliminated.

A somewhat similar theoretical approach reported by Gail ter Haar and P. Carnochan was applied both to 27-MHz rf inductive heating and to u-sound for comparative purposes. Experimental verification was done with a plane parallel model rotated about an axis parallel to that of the incident beam.

The theory of thermal conversion of u-sonic energy appears to be less satisfactory than that for rm-waves. According to Chivers, speaking for P.A. Lewin and R.C. Chivers, there is still no adequate model for cells and tissues. Viscoelastic interactions corresponding to the several familiar models may be complicated by resonances within whole organs and individual cells. For this reason, the variation of attenuation with frequency depends in a complicated way upon relations between the various relaxation times and resonance periods and the characteristics of the incident u-sound. Chivers felt that while there are plenty of equations there is a poverty of numbers to put into them. As an aside, while on the matter of resonances, I might mention that A.P. Servazyan reviewed biological resonances over the whole range from feedback-generated oscillations in enzyme reactions to slow oscillations, with a

period of weeks or months, in the human lymphocyte count. He made the (to me) illuminating point that resonance will be excited by energy input of any kind provided it is of the correct frequency. This observation, if pursued, might have provided a unifying idea for some of the discussions, for it would suggest that parallels between pulsed u-sound and pulsed rm-waves of similar pulse characteristics might well be sought experimentally.

K.D. Wien and D. Harder drew attention to the fact that, if pulsed ultrasound is applied to a surface transducer, the true pulse duration depends upon the axial distance from the transducer and position in the radial field. This arises from large phase differences between wavelets arriving at a given point from different points of origin on the surface of the transducer. Thus sharp extrema are exhibited in the near field, both in the axial and the radial sections. These are averaged out if the dose is integrated over the cross section of the transducer. Extrema become less pronounced at distances beyond the near field.

(4) Temperature Distribution in Models

Most people try to use models to confirm the predictions of their phantoms, or else they use phantoms in order to broaden the very limited range of parameter values readily accessible to experimental study. The limitations arise from restrictions on the rm-wave frequencies legally available and from difficulties in simulating the properties of living tissues with the materials available. Observing the legal limitations, temperature distributions in rf fields of 434 and 2,450 MHz in a "muscle equivalent" gel with simulated fat layer were reported by B.M. Southcott et al. M. Herbst and J. Bernhardt used capacitative heating at 13.56 MHz from a short wave generator with a cooled applicator and various models intended to simulate head and lungs.

An interesting example of the use of experimental data derived from models as a basis for programming local hyperthermia therapy was provided by K. Hynynen et al. The tissue simulants were suspensions of graphite in a gelatin gel. These had the shortcoming that the gels that reproduced the u-sonic attenuation coefficient of "average" living tissue had three times their thermal conductivity. Nethertheless, as the study was concerned mainly with comparative observations on different transducer orientations and different simulated blood flow rates, the results may have furnished a valid basis on which to develop a computer program. The factors varied included combinations of three plane transducers, a focused source, and leveling of temperature peaks by rotating the transducers. In some arrangements the flow of blood shifts the temperature peak to greater depths. If the beam is focused, on the other hand, blood flow in the focal region produces more cooling there than elsewhere, for obvious reasons, and thus, presumably, moves the peak to a shallower position.

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(5) Measurement of Temperature

A problem that has always bedeviled workers in the field of u-sonic and rm-wave therapy, whether using models or attempting *in vivo* observations (but not a major source of apprehension for phantoms and their masters) is the measurement of temperature. Metal probes distort the field and, reciprocating, the field probably invalidates the probe's temperature message. The obvious approach is to switch off the field, measure the temperature, and apply some sort of plausible extrapolation to zero time. An example can be found in the work of J.W. Hand already cited. Artifacts arising from the use of thermocouples at 434 MHz were discussed by B.M. Southcott.

It has been thought that if blood flow through an irradiated region were adequate, measurements of the temperature and flow rate of the affluent blood could be used to calculate the average temperature of the heated tissues. This is an upside-down version of a principle long used by physiologists to measure blood flow by introducing a known amount of heat into the tissue. Indeed, a diathermy generator was used by Wever and Aschoff (1956) as the source of heat. The proposed application would therefore require measurement of blood flow by an independent method such as clearance of radioactive xenon. It is difficult to see that these procedures would ever become simple enough to qualify for routine use. In discussion it was stated that the xenon washout time does not, in fact, correlate at all well with the thermal washout. In any case, it was thought that local temperatures are needed, rather than some regional mean. Also, as the circulation within tumors is diffuse, it is unsuited to washout techniques. A more impatient objector remarked that it was imperative to press ahead with hyperthermia therapy without waiting for ideal information. This sentiment emerged several times during the conference, when it seemed that the research people were parading (rightly, in my view) the obstacles they were tilting at.

Two recent developments show much promise. The first is a noninvasive procedure developed initially for the diagnosis of conditions accompanied by locally raised temperature (Gautherie et al., Robert et al., Nguyen et al., all 1980) based on the black body emission properties of tissues. It is a microwave imaging system, operating in the 2 to 70-GHz frequency range. Contact and remote sensing versions have been used successfully. The device is better than infrared imaging systems, especially on account of the transparency of bone at some m-wave frequencies. M. Gautherie stressed the need for further work on models, presumably by means of a frequency scanning procedure. Although this technique will not provide the complete spatio-temporal picture, the loss of resolution may be a price worth paying for the convenience of noninvasiveness.

The second development concerns a field-independent temperature probe that will probably supersede the well-known liquid crystal probe,

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which is too large for many purposes and by no means easy to use (Rozzell et al. 1974; Samsel and Gautherie 1980). The new device, still under development, was described by K.A. Wickersheim and R.V. Alves. The sensor is a europium-activated gadolinium oxysulfide phosphor that emits two sharp fluorescent lines when activated by ultraviolet radiation. The intensities of emission of the two lines differ in their temperature dependence because they arise from different excited states of the europium ion. Consequently, their ratio can be used as a measure of temperature unaffected by nonthermal disturbances. The output, which is nonlinear, can be calibrated over the range -50 to +250°C. The phosphor is in the tip of a fiber-optic probe less than 0.8 mm in diameter. The exciting radiation is pumped down the fiber. If, as projected by the inventors, a multisensor probe can be devised, an instrument that would be suitable for work with models, and possibly also for detailed clinical monitoring, may be at hand. Quite another question is that of cost: how many people will be able to afford it? Most will have to wait for a cheaper application of a simpler physical principle, and there is reason to be confident that the wait will not be long.

(6) Biological Aspects of Hyperthermia

Having succeeded in introducing heat into the body more or less where we feel it is needed, we confront an array of possible side effects. These may be irrelevant to the clinician using hyperthermia semiexperimentally as a last resort on the terminally ill, but if hyperthermia is to have a future in less-extreme circumstances, the side effects must be known and their importance assessed in relation to the total effectiveness of the treatment. "Side effect" is, perhaps, a misnomer when one really means to suggest physiological reactions occurring in some part physically remote from the area of interest, as simplistically defined; it must always be kept in mind that side effects may feed back in such a way as to alter the reactions expected on purely physical grounds.

The full range of the effects of local hyperthermia on the cardiovascular, hematological, endocrinological, neurological, immunological, and even genetic functions cannot be appreciated from the necessarily limited coverage afforded it at a physically oriented conference. The main contribution was in the nature of a review, albeit of a restricted field. S.M. Michaelson referred rather particularly to the physiology of temperature regulation and the way heat stress may modify control of thermogenesis by the hypothalamus and other neuroendocrine systems. Michaelson, with others, has reviewed the neuroendocrine aspects of m-wave exposure in more detail elsewhere (1975). Clearly, changes in internal temperature gradients induced by feedback from remote regulatory centers may modify the degree and distribution of local hyperthermia produced by m-waves or u-sound and must be taken into account in translating the results of model experiments and phantom calculations to anticipated effects *in vivo*.

Tissue cultures provided the evidence for another kind of biological effect of hyperthermia. Its applicability to man is yet to be demonstrated. Two groups working in the US reported on the emergence of new protein components in Chinese hamster cells after brief heating at 45°C. There was an apparent correlation of the presence of these proteins ("heat shock proteins," HSP) with increased resistance of the cells to thermal damage ("thermotolerance"). Similar techniques were used in the two studies. The cells were heated and then incubated at 37°C. At various times during this incubation they were labeled with ^{35}S methionine and the incorporated label fractionated on a sodium dodecyl sulfate gel. Parallel measurements of survival rates, presumably after repetition of the heat shock, were made by counting the viable cells. Gloria Li and coworkers saw three HSP bands while J.R. Subjeck et al. found six, but the two groups agreed as to the molecular weight of the main component, 68,000 daltons. It was not clear whether these proteins were totally absent from normal cells, or whether their concentration was merely much enhanced by heat shock. Subjeck et al. showed that *de novo* protein synthesis was involved when they found it to be inhibited by actinomycin and cycloheximide, but this did not quite answer the question. They went further than Li in concluding that the HSPs represent the expression of heat shock genes widely dispersed among different organisms and in assigning to them, therefore, a fundamental but unknown biological role. All this lends some weight to the idea that thermotolerance may have to be taken into account when heat therapy is administered.

(7) Therapeutic Uses of Hyperthermia

At a conference dominated by participants from departments of radiology, oncology, physical medicine, surgery, medical physics, bioacoustics, radiation hygiene, and dermatology, one might have expected to see some persuasive evidence of clinical success in the use of hyperthermia. In point of fact, however, only a few cancerous rodents emerged. In his tutorial, N.M. Bleehan had made it clear that controlled delivery of heat where it is most needed—supposing we know where that is—is beset with much more imprecision than is the case with ionizing radiation. Bleehan gave the impression that, despite a long and checkered history, heat therapy is still in its experimental infancy, especially when applied to deep-seated malignancies.

Rats and mice were the subjects of several reports. The most notable report, in the author's opinion, was that of F.W. Kremkau. Previous work had shown that certain mouse tumors heated by u-sound or by immersion in a water bath shrank instead of continuing steadily to increase in volume. The mice were not "cured," because tumor growth was resumed later. Kremkau used mouse tumors of seven different types as well as normal mouse tissue subjected to X-irradiation combined with continuous or pulsed u-sound *in vivo*. For a subcutaneous tumor in a hind limb, it was found that the X-ray dose required to inhibit half the tumors ("tumor control dose," TCD50) was decreased by continuous

or pulsed u-sound at 1.9 MHz, average power density 1.5 W cm^{-2}. The "therapeutic advantage," in Kremkau's words, may be slight for several reasons. The temperature in the treated tumors is lower at the edges than inside, so that continued growth may occur even when most of the tumor is controlled. Normal tissues were no less sensitive than the tumors, so that they would need some form of protection. Cooling the skin helped to avoid skin reactions to X-rays, which tend to be worsened by heating. Heat applied after X-irradiation, rather than concurrently, offered some apparent advantage.

Other combinations of treatments of rat tumors were reported by G.M. Hahn et al. and by F. Zywietz. Hahn's work included cell survival measurements *in vitro* and tumor growth inhibition *in vivo*. The drug-dose-survival curves *in vitro* were extremely sensitive to heat, with an abrupt increase of sensitivity between 41 and 43°C. From the calculated enthalpy change, Hahn concluded that alkylation and lysis is the primary mode of cell killing by amphotericin. Heating apparently induced some thermotolerance in cells treated with actinomycin D. The experiments with leg and flank tumors in rats involved measurement of drug-induced growth delay with or without hyperthermia brought about with hot water, u-sound, or r-waves. "Cures" were obtained when flank tumors were treated with certain drugs, for example, bleomycin, plus radiation. U-sound seemed to be more effective than rf radiation. Leg tumors were less readily "cured," possibly because of less effectively heated regions near the bone.

Zywietz, like Hahn, measured the growth delay. The tumor used by him was a rhabdomyosarcoma growing in the rat flank. Heating the m-waves, 2,450 MHz, had little effect. Growth delay produced by 200-kVp X-rays (15 and 30 Gy) was enhanced by heat treatment. Volume regression was also favorably affected. Questioning elicited the fact that no biopsies had been done.

Superficial tumors in man, as in rat, present an opportunity to conduct more effectively controlled studies than do those that lie deeper. In the work of C. Marchal et al., attention was given to superficial nodules that often occur in groups, so that some could be left untreated. In one set of experiments some of the nodules were heated with u-sound, 1 to 3 MHz, applied to the skin, with or without chemotherapy or radiotherapy. The depth to which the hyperthermia reached was increased, when necessary, by means of an array of six transducers. Temperature was measured with thermocouples introduced through catheters or applied to the skin. Some of the treated nodules were said to have regressed, and this was supported by photographic evidence. In another series, hyperthermia was generated by m-waves at 434 MHz, with or without "low doses" of ionizing radiation or drugs. Regressions were noted only when radiotherapy and heat were given together.

III. PRE-THERMAL EFFECTS ON NONIONIZING RADIATIONS

(1) Pre-Thermal Ultrasonics

Intentionally or not, the conference was weighted on the side of u-sound, especially in the sessions on low-level effects. The ratio of about 20 to 4 for papers touching on the prethermal effects of u-sound and rm-waves respectively can be interpreted as a tacit endorsement of the reality of the former and an inclincation to consider the latter slightly liable to subvert conventional doctrines. It is indeed true that prethermal mechanical events are well documented and more justly suspected of being inimical to the beneficial effects of hyperthermia. The bugbear of u-sonic therapists, however, is cavitation. The question was repeatedly asked, when a particular thermal phenomenon was reported, whether it might not have been due to cavitation. The reply, in just one instance, that compression to two atmospheres had no effect, was not convincing.

Another assertion, that cavitation would not occur in the absence of dissolved gases, was more favorably received but still open to question. The calculated negative pressure needed to create a 4 Ångstrom hole in water is indeed high (about -10,000 atm); but holes of approximately this size arising spontaneously by fuctuations in the structure of water would facilitate rupture by several orders of magnitude, as would the presence in biological tissues of innumerable discontinuities of low interfacial tension. Nevertheless, dissolved gas would certainly increase still more the probability of cavity formation and would favor the rapid decrease of pressure within the bubble as the size increases, with consequences mentioned in C.R. Hill's tutorial. If the gas does not have time to redissolve during the adiabatic compression phase, the bubble will grow by "rectified diffusion," eventually reaching a size at which it will resonate with the u-sound. R.E. Apfel gave the respective resonant diameters as 6.0 μm at 0.5 MHz, 3.2 μm at 1.0 MHz and 0.55 μm at 8 MHz. On the other hand, if collapse does occur, a very high local transient temperature will result, with disturbance of electric double layers, accumulation of charge by a sort of Wimshurst or Van de Graaf mechanism, and *de novo* formation of ions and free radicals. Apfel reviewed cavitation from the point of view of what is physically possible.

Moving from the physically possible to the unequivocally demonstrable, W.L. Nyborg considered cavitation and prethermal effects of u-sound at the micron, or cellular, size level. Quite varied phenomena testify to the increased susceptibility to cell injury when bubbles appear as a result of low-level irradiation in the MHz frequency range. Blood platelets accumulate and are damaged around the pores of membranes when bubbles are present. Adenosine triphosphate is released from red blood cells. The leaves of *Elodea* are killed when exposed to weak u-sound at the resonance frequency of the gas in the gas channels. There are

also various nonoscillatory microstructural effects in the vicinity of vibrating bubbles. These include accumulation of particles around the bubble, cell distortion leading to lysis, cytoplasmic streaming and formation of a microtrabecular mesh in solid tissues. The effective gravitational acceleration around a bubble can be very large, e.g., 3×10^8 cm^2 s^{-2}, because the determining second order term is proportional to ν^2/r^5 (ν is frequency, r is bubble radius).

Some of the same phenomena were discussed by Mary Dyson, who described her experiments (beautifully illustrated in a movie) on intravascular stationary waves evinced by the banding of red blood cells, within a few tenths of a second, at intervals of half a wavelength. Apparently the plasma continues to flow more or less unhindered through the forest of red cells. Dyson referred to other prethermal phenomena possibly of importance in u-sonic therapy: vesiculation of endothelial cells, extravasation of red cells, and stripping of particles by high-velocity flow. The complicated summation of these effects, to which might be added transient damage caused by cavitation, could result in facilitated tissue repair rather than further injury. Dyson and her colleagues have had much success with u-sonic therapy of otherwise intractable ulcers.

A tropical fish with a very thin, flat tail (100 μm) provided C.J. Martin et al. with an excellent preparation for observing blood stasis, cell rotation, and microstreaming in u-sonic fields. The tail of *Xiphophorus maculatus* has two parallel lengthwise sets of segmented rods of cartilage with transverse supports. An afferent blood vessel runs down the middle of the tail, and blood is returned through two vessels outside the longitudinal rods. There are short circuits here and there. In the experiments, u-sound (0.75 or 1.5 MHz) was obliquely incident on the tail. The effects were watched in the light microscope. Single cells and cell clusters were seen to rotate at about 4 s^{-1} and the blood vessels became obstructed near the transverse connections. The threshold intensities were strongly dependent on frequency.

In two papers, Gail ter Haar brought the subject of cavitation into the framework of medical research on u-sonics. Of the four methods she listed for detecting cavitation, she chose acoustic subharmonic emission as most suited for work with cells and tissues and u-sonic imaging for observations on animals. Chinese hamster lung fibroblasts were monitored for cavitation during exposure to u-sound at 1 MHz. Cell damage was detected by trypan blue staining and colony counting. Total cell numbers were measured in the Coulter counter. Good exponential survival curves were shown. A well-defined threshold for loss of viability and for cells in the S1 phase occurred at an intensity of 0.25 W cm^{-2}, and this correlated well with subharmonic emission. The work with animals was aimed first at finding a reliable way of detecting and locating bubbles. To do this, guinea pigs were given decompression sickness ("bends") by compression and decompression. Bubble sites were located by a superimposition technique using an 8-MHz u-sonic scanner. Changes

in the images during decompression could then be ascribed to the presence of bubbles. In the next stage, cavitation was produced in guinea pig legs at atmospheric pressure with 0.75-MHz u-sound at 0 to 3 W cm^{-2} therapeutic intensities. As would be expected, subcutaneous fat was a preferred site for formation of bubbles. The next place, at higher intensity, was muscle. There was some evidence of intravascular bubbles.

The results give rise to some concern about the safety of therapeutic u-sound. As long ago as 1944 Gersh et al. (1944, 1945) showed that bubbles in adipose tissue caused disruption of fat cells and mobilization of depot fat in the blood. Later work by others showed the presence of fat emboli in the lungs, livers and kidneys of decompressed dogs and men, as well as rheological changes resulting in vascular damage and formation of fibrin thrombi.

A popular method for the investigation of prethermal effects, and one pertinent to the possibility of their therapeutic exploitation, is to sensitize the system to another stress to the point at which a small superimposed nudge will tip the balance in favor of a large and easily observable change. Though not described in quite these terms, this was essentially the approach used by Gail ter Haar and I.J. Stratford, who compared the dose-survival curves of Chinese hamster lung fibroblasts irradiated with u-sound (3 MHz) at 43°C with the curves obtained at the same temperature without u-sound. The u-sound intensity that was used produced no killing when applied at 37°C. The slope of the 43°C survival, curve, log (N/N_0) against time, was increased by the u-sound to an extent far greater than could be explained by the associated temperature rise of only 0.2°C. For data obtained at several different temperatures, the Arrhenius plots gave non-parallel lines. The enhancement of lethality caused by u-sound became more pronounced when the radiation was pulsed at intervals of 1 μs to 1 ms. Another point favoring a prethermal mechanism was the finding that thermo-tolerant cells were not protected against u-sonic killing.

The same device was used by Kremkau, the major stress in his work being provided by drugs. These were applied *in vitro* to mouse leukemia cells subsequently assayed by inoculation of mice and monitoring of the animals' survival. U-sound alone (2 MHz, 10 W cm^{-2} for about 10 min) had no effect, but when it was combined with chemotherapy there was a large increase of host survival time, provided the irradiation took place within 5 min of giving the drug. In other cases (5 drugs out of 10 studied) no increase of survival time was evident. There was no obvious relationship between the mode of action of the drugs and the effect of irradiation and no influence of u-sonic treatment on subsequent susceptibility. As heating by other means was without effect, the action of u-sound was presumed to be prethermal.

Biological manifestations of u-sound effects other than cell death, with or without supplementary stresses, received comparatively little attention. N.C. Barrass and Gail ter Haar exposed synchronized diploid

cells derived from BHK 21 C13 to u-sound (3 MHz, 3 W cm^{-2}) at 37 or
43°C. Using a differential staining technique they were able to count
cell numbers over three generations, finding that u-sound at 37°C delayed
the second and third mitoses. They also counted sister chromatid ex-
changes. Though these were very sensitive to handling, it was possible
to conclude that the mean frequency of sister chromatid exchanges at
43°C was increased by u-sound. A speaker from the floor remarked that
the container used for the cells should have been made of freshly blown
glass to avoid cavitation.

Increased frequency of sister chromatid exchanges in cultured cells
was among the many effects of quite low level (15 mW cm^{-2}) pulsed u-sound
discussed in the abstract by D. Liebeskind et al. Liebeskind reported
other effects on 3T3 mouse fibroblasts, notably the increased numbers
of perichromatic granules in all cells, an extraordinary increase of
mobility (shown in a movie) and a decrease of contact inhibition. The
changes persisted for about 10 cell generations after irradiation.
This the authors find disturbing. They say in their abstract that if
similar things occur *in vivo*, which is not yet known, subtle damage
to fetal cells "might affect cell migrations during ontogenesis; if germ
cells were so involved, the effects might not become apparent until
the next generation."

Liebeskind had mentioned disturbances of phago-kinetic tract patterns
in vitro. Involvement of the reticuloendothelial system *in vitro* after
exposure of rats to u-sound (1.65 MHz, 1.37 W cm^{-2}) was indicated by
the results of A.H. Saad and A.R. Williams. Clearance curves for sulfur
and graphite particles were measured by labeling with technetium 99 ^{m}.
There appeared to be a threshold intensity below which no change could
be established. Above the clearance rate threshold the clearance time,
$t_{0.5}$, increased linearly, for example, from 1 min without irradiation
to 3 mins after a 5-min exposure. The distribution of particles among
the main deposition sites—liver, lungs, and spleen—was unaltered.

To conclude: the impression gained at the conference was that
a good deal is known about prethermal mechanisms of u-sound action
and their manifestation in the immediate behavior of cells and tissues.
The remoter consequences, which may well be numerous and complicated,
are less well documented and still less satisfactorily evaluated with
a view to their avoidance or exploitation in the medical applications
of u-sound. The possibility of long-term injury must not be ignored.
On the other hand, there may be occasions when a little judicious local
agitation may speed up such desirable processes as the healing of wounds,
ulcers, and fractures. Unfortunately, there is little prospect that
anything approaching true selectivity at the cellular or macromolecular
levels will be achieved.

(2) Prethermal Effects of Radiowaves and Microwaves

It was remarked earlier in this report that the prethermal effects
of rm-waves received little attention at the conference. One reason

for this was that only two of the people perhaps best qualified to speak
on the subject were in attendance. A more important reason, however,
lies in the nature of these phenomena. Obviously, in any experimental
setup involving u-sonic irradiation or other nonionizing irradiation
of finite duration exceeding some very brief lower limit, prethermal
processes occurring at any given instant will coexist with heat production
stemming from antecedent pre-thermal events. In the case of u-sound
on the one har... the pre-thermal events can, with some confidence,
be unscrambled from the mixture, so that experimentation is not confined
to conditions under which rise in temperature is negligible. On the
other hand, with rm-waves of frequencies less than those capable of initi-
ating clearly photochemical actions, the primary processes are conven-
tionally thought unable to lead to any considerable biological distur-
bance. Insofar as they are not really understood, they are subject to
controversy, with the odds weighted on the side of conformity. It is
held that heat is so much more potent biologically than any immediately
obvious nonthermal event brought about in this frequency at extremely
low field strengths. It might follow that prolonged exposure would be
necessary on the possibly fallacious ground that it is the total dose
that matters. The difficulties then become formidable. Proof must
be supplied that heat production and dissipation are such as to pre-
clude biologically significant changes of temperature anywhere in the
system. There is, too, an almost limitless range of possibilities in
selecting the physical parameters of the incident radiation and the
biological parameters to be recorded. If resonances are involved, the
chances of hitting on one purely by random measurement without the
benefit of any guiding theory are remote. Further, both sets of pro-
perties are likely to be subject to instabilities comparable to the
respective noise levels and their mutual influence.

P. Czersky is a recognized authority on the long-term effects of
ambient electromagnetic pollution on the population at large and on
occupationally exposed persons in particular. Although he was announced
on the program, Czersky did not attend, so a good deal of challenging
work, much of it issuing from Poland and the USSR, went unreported.
Some of the work is reviewed by Barański in the book he wrote with
Czersky (1975), while some of Czersky's experimental work describing
subtle effects on the lymphocytic system and the erythroblastic cell
line is conveniently available (Czersky 1975). Conferences at which
Czersky was present have been reported previously (*ESN* 31-11:435 [1977];
ESN 32-3:85 [1978]; *ESN* 32-11:363 [1978]; ONRL Report C-14-77).

In Czersky's absence, prethermal effects of a different kind from
those affecting human populations were described by H.P. Schwan. These
arise from the ponderomotoric forces to which particles are subjected
under the influence of alternating electrical fields. The forces become
important when their energy exceeds kT, so that threshold field strengths
exist for the phenomena elicited, dependent upon particle size, shape,
electrical properties, and other factors. At the cellular level, particles
may be translocated (dielectrophoresis), oriented, aligned (pearl chain

formation), deformed, fused, or lysed. The resemblance to the list of prethermal u-sonic changes is, of course, not accidental. A detailed comparison cannot be undertaken here, nor is it necessary, because published descriptions and accompanying theory are available, largely from Schwan's laboratory. One may simply mention as examples the "flip-flop" of ellipsoidal particles at two turnover frequencies, implicit in the theoretical study of Saito et al. (1966) said by Schwan to have been demonstrated with *Paramecium* by Heller. In highly inhomogeneous fields, membrane breakdown (Zimmermann et al. 1974) can be put to good use in causing cell fusion. Schwan said that this had been repeated so as to manufacture a giant red blood cell from 100 ordinary ones. Perhaps it should be called cytopolymerization, and perhaps a new brand of biotechnology will emerge. We have here, speculation aside, a series of prethermal changes of potential biological significance as initiators of biological change *per se* and as currently feasible contributions to bioengineering. One thinks of the use of dielectrophoresis in measuring cell surface charge density, described in a book by Pohl. And long ago Fuerth took advantage of the field orientation of an ellipsoid to measure the dielectric constant of the ambient medium—a much-neglected method that should find use in the study of macromolecular systems. As for the impact of ponderomotor forces upon medical research, Schwan had concluded earlier (Schwan 1964) that they "appear to have no biological significance for human beings exposed to a 'thermally safe' microwave field." The reasoning, backed up by quantitative argument, was that under such thermally safe conditions the superficial structures of the body, which are subject to the largest gradients of electric field strength, contain no freely movable particles that could respond to the applied force. At greater depths, where the critical relationship between particle size and frequency might exist, the gradients would have become much too small.

The paper by W. Grundler and colleagues moved far away from ponderomotor forces to whole organisms growing in m-wave fields. The phenomena they described have all the earmarks of resonant responses, manifested by the inhibition and stimulation of the proliferation of yeast cells. The essential findings have already been published (Grundler and Keilmann, 1978). The paper given in Oxford was important because, in the face of much criticism, the authors have persisted in doing better experiments and have thereby confirmed their own published results. This is not quite as good, perhaps, as a totally independent repetition by other workers in another laboratory, but it must be taken seriously. It seems that over the applied monochromatic frequency range 41.640 to 41.835 GHz the growth rate of yeast cells in an aqueous medium may vary by ± 20%. This is not random variation nor is it irregular. It is periodic with frequency. Over the quoted narrow range of frequencies there are about 6 cycles of growth rate change of band width around 10 MHz. The increases of temperature under the prevailing irradiation conditions were about 0.2°C, which alone would have caused the growth rate to increase by only 0.2%.

Unfortunately, there was not sufficient time to discuss Grundler's findings. It would have been interesting to hear questions and comments on the extraordinary technical refinements needed to achieve the long-term frequency stability reported. This was about + or - 1 MHz, or 5 parts in 100,000. The theoretical aspects should have been mentioned, for the mere hint from a competent theorist that a phenomenon might be expected would make it seem less exotic. Several theorists are, in fact, concerned. One of the latest contributions appeared only after the conference had ended. Putnam et al. (1981) predict a number of m-wave resonances in the terminal region of the DNA double helix. These are broader than those found by Grundler and Keilmann and, for the most part, more widely spaced. This gives the experimentalists something to look for with dielectric scanning and Raman spectroscopy.

There was an interesting paper by J. Sciandra and colleagues, who measured the effects of m-waves, 915 MHz, on the rate of enucleation of rat erythroblasts (metarubricytes). The cell suspensions were kept at constant temperature with water circulating through the wave guide and antenna system. Whereas the enucleation rate increased with rise of temperature, the rate was decreased by irradiation at constant temperature, both at 37 and at 41°C. The alkaloid cytochalasin B, which inhibits microfilament movement, was used in an attempt to clarify the mechanism of the effect: can it be localized on the membrane, or more specifically on the enucleation zone? The results seemed inconclusive at this stage but the system is an admirable one for further study.

APPENDIX I

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